PROTOCOL DOCUMENT DEVELOPMENT:

DCP Guidelines for Phase I/II Trials of Chemoprevention Agents

Protocol Document Requirements during the Solicitation and Post-Award Period

As stated in the Request for Proposal, a clinical protocol document shall be provided with the technical proposal. This "Protocol Development Document" presents the recommended format and required content for the preparation of this document. During the competitive source selection those Offerors deemed in the competitive range may be asked to respond to questions from the DCP Technical Evaluation Panel to improve and strengthen their proposal and to make the corresponding changes in the protocol document.

Following contract award, the Contractor will have **30 calender days** to submit the following documents to the DCP Protocol Information Office:

1) Draft of the final protocol document
2) Informed consent form
3) Study-specific Case Report Forms

Following review of these documents, the DCP will either give final approval or request further revisions to the document. Any revisions requested must be returned to the DCP Protocol Information Office within **30 calender days**. If applicable, the protocol will be submitted under a DCP-sponsored IND. The clinical trial will be initiated at the direction of the NCI Project Officer only after Food and Drug Administration (FDA) approves the protocol, IRB approval has been documented, and the drug is available and secured for the specific Contractor trial.

General instructions for protocol document development:

This Appendix details the required components for clinical trials of chemopreventive agents. This document is divided into sections that correspond to the required protocol sections. Examples of recommended language to be incorporated in the protocol are included. In specific areas (case report form development, biomarker methods development), this document will refer the reader to another Appendix where this information is available in detailed format. This document may also refer the reader to other existing web sites for information (i.e., Common Toxicity Criteria, Informed Consent).

All changes made prior to protocol activation will be referred to as "VERSIONS". All protocol document changes made following protocol activation will be referred to as "AMENDMENTS." Therefore, the original document submitted to the NCI for first review (response to solicitation) is

Version 1.0. A protocol submitted to NCI the second time for review is Version 2.0 and so on. Following study activation by the NCI, the first approved change to the protocol document is Amendment 1.0. Please use this naming convention for all protocol documents submitted to the DCP. *All protocols submitted for review shall include a footer on each page of the protocol which includes NCI protocol number, date of submission to the NCI, and current version number of the protocol.*

Submission of the protocol to NCI, Division of Cancer Prevention

Electronic submission of protocol documents is encouraged. The document can be sent as an e-mail attachment in MS Word or WordPerfect. Documents may be e-mailed to the DCP Protocol Information Office at: **parrecol@mail.nih.gov**

If hard copies are being sent, please mail 3 (three) copies to:

Linda Parreco, RN, MS
Protocol Information Office
Division of Cancer Prevention
9000 Rockville Pike
Executive Plaza North, Suite 300
MSC 7340
Bethesda, MD 20892-7340

Alternate address for express mail by hand delivery:

Executive Plaza North, Suite 300
6130 Executive Boulevard
Rockville, MD 20852

Questions regarding the submission of documents may be directed to the DCP Protocol Information Office at (301) 496-0265. The Principal Investigator will be contacted via e-mail to confirm that the protocol document was received by the PIO and will be provided a projected time line for the DCP protocol review process.

COVER SHEET TEMPLATE

Title of Protocol

Principal Investigator
Institution
Address, Phone Number, Fax, E-Mail

NCI Contract/Grant Number:

Name and location of study site(s) or institution(s):

Date of current protocol submission and version number:

Date of previous submission dates and version numbers:

Name(s) of study agent(s):

IND number/IND holder (if applicable):

PROTOCOL SYNOPSIS TEMPLATE

TITLE OF PROTOCOL:				
NCI CONTRACT/GRANT NUMBER:				
DCP WORK STATEMENT NUMBER: DATE OF AWARD:				
LOCAL IRB PROTOCOL NUMBER:				
PRINCIPAL INVESTIGATOR:				
INSTITUTION (NAME AND ADDRESS):				
CO-INVESTIGATORS:				
STUDY CENTER(S):				
Study Agent(s)	Formulation	Dose	Regimen	Route
Study Design (including phase of development, objectives, diagnosis and main entry criteria):				
Methodology (including endpoints, laboratory tests, sample collections):				
Proposed Entry Date First Subject: _____	Total number of Subjects planned: _____	Proposed Accrual Rate (subjects per month): _____	of	
Estimated number evaluable: _____	Estimated number withdrawals: _____	Average # subjects Per site: _____	Estimated # CRF's per Subject: _____	
Estimated enrollment period:				
Duration of Treatment:				
Follow-up:				
Method of Monitoring (circle one): DCP Monitoring Contractor Institutional monitoring				

SCHEMA TEMPLATE

Protocol Title

Name of Principal Investigator and Institution

Subject Population (*e.g.*, women with newly diagnosed CIN III)

9

Randomize to X mg drug A or placebo qd for 6 months (3-day holiday/month) (25/arm)

9

Summary of evaluations to be conducted and time points (*e.g.*, Repeat colposcopy at 3 months; colposcopy with biopsy at 6 months; pap smears at 3 and 6 months)

9

Summary of endpoints (histological response of CIN; modulation of intermediate biomarkers)

TABLE OF CONTENTS TEMPLATE

1.0 OBJECTIVES

Study objectives are concise statements of the primary and secondary clinical and statistical questions the study is designed to answer. Each objective should be stated as specifically and succinctly as poss Both primary and secondary hypotheses must relate to the hypotheses presented in the rationale (sect 6.0) and should be consistent with the objectives described in the statistical section (section 16.0). C differentiate primary and secondary objectives. Number objectives in order of priority or importance

1.1 First objective/hypothesis
1.2 Second objective/hypothesis
1.3 Third objective/hypothesis

EXAMPLE: To evaluate the effects of a daily dose N of drug E in population X on parameters Y and Z b continuous or daily recording of results obtained in tests A and B during time period C, as compared with drug D at dose E, under the same experimental conditions.

Do not write that the objective is "to determine the mechanism of action of drug X"; this objective is too general, vague, and merely restates the overall goal of the study.

2.0 BACKGROUND AND RATIONALE

Provide sufficient background information to describe the rationale for the study. Present possible mechanisms and/or theoretical framework for conducting the study. Include relevant literature review pertinent preclinical, pilot, and preliminary and/or unpublished data to support conduct of the propose study. Clearly state hypotheses for the primary and secondary objectives (Section 5.0). Justify select the target population, chemopreventive agent(s), and study endpoints (*e.g.*, specific surrogate endpoint biomarkers), the choice of particular techniques for endpoint assessment and measurement of drugs, metabolites and drug effects.

3.0 SUMMARY OF STUDY PLAN

For the convenience of the reader, this section should provide a brief synopsis of the following points should be a brief narrative of the study schema in Section 3.0.

- Study design (*e.g.*, double-blind, placebo-controlled, multi- or single center, Phase I, II).
- Number of subjects to be enrolled (total number and number per arm).

- Brief description of the subject population.
- Treatment plan, including treatment groups, dose(s), and duration of exposure to study drug.
- Description of run-in period, if applicable
- The points at which subjects will be assessed.
- Description of measurements taken to meet study objectives.

- Description of clinical procedures, lab tests or other measurements taken to monitor effects of st drug on human safety and to minimize risk.
- Duration of follow-up.
- Duration of study.

4.0 SUBJECT SELECTION

4.1 Study Population:
Defines the composition of the study population, including:

- Health status as related to cancer (*e.g.*, healthy volunteers, persons at increased cancer risk, subjects with prior cancer diagnosis).
- Anticipated demographic make-up (*e.g.*, age and gender) of subjects to be enrolled. Include estimated targets for gender and minority inclusion, as per NIH Guidelines. Where appropria address the inclusion or exclusion of children, as per NIH Guidelines. This section should demonstrate that the study population is appropriate (e.g., a chemopreventive drug can modul tissue being evaluated, population is sufficiently homogeneous to allow meaningful analysis endpoints, appropriate risk status or disease stage, etc.)

4.2 Participating Centers:
If multiple facilities (*e.g.*, centers, clinics or hospitals) are participating in the study, all should identified specifically in this section.

4.3 Sources or methods of recruitment:
Describe source of study populations and methods for identifying and recruiting them (e.g. me high-risk clinic rosters, cancer registry, physician referrals, etc.) Plans are specified for gende minority recruitment, as per NIH Guidelines.

4.4 Method of subject numbering:
Describe method of assigning subject numbers.

NOTE: It is preferable for a site to identify and use one unique subject number throughout the s regardless of the phase the subject is in.

4.5 Inclusion Criteria:

Inclusion criteria are comprehensive, unambiguous, and not unnecessarily restrictive. For each provide methods for assessing inclusion criteria (e.g., risk assessment tools, clinical evaluation pathology review criteria, etc.).
These criteria include the following:

- Specific health risk or disease requirements (*e.g.*, age, Eastern Cooperative Oncology G (ECOG) performance status, life expectancy).
- Health status requirements
- Organ function parameters
- Other areas specifically relevant to the methodology of the study

NOTE: Provide histologic confirmation of diagnosis, time from diagnosis, and disease status at entry (or extent of disease) for cancer subjects or subjects with precancerous lesions.

EXAMPLE: Inclusion Criteria:
1. Is the subject over 18 years of age?
2. Does the subject have an ECOG Performance Status of 0-2?
3. Has the subject been properly informed of the study and signed the Informed Consent?

4.6 Exclusion Criteria:
Exclusion criteria are comprehensive, unambiguous, and not unnecessarily restrictive.
These criteria include:
- Contraindication to participation based on agent pharmacology and metabolism, toxicology, clinical and methodology considerations.

NOTE: Healthy volunteers may be required to demonstrate absence of chronic medical conditions regular use of certain medications.

EXAMPLE: Exclusion Criteria:
1. Use of any nonsteroidal anti-inflammatory agent within two weeks prior to enrollment.
2. Participation in another chemoprevention investigational study within one month prior to enrollment.
3. A history of smoking within one month prior to enrollment.
4. Active malignancy at any other site.

5.0 AGENT INFORMATION AND ADMINISTRATION

5.1 Name of Agent. If indicated, include IND number and Sponsor.

5.2 Dose Groups and Duration of Exposure

5.3 Dose Selection: Describe the method and data supporting the dose(s) to be administered.

5.4 Formulation
Include:
- Agent formulation to be used (*e.g.*, oral)
- If alternative formulations are available, justify why the chosen formulation will be used for t study.
- Description of the agent (*e.g.*, gelatin capsules, clear liquid)
- List of ingredients in the vehicle/excipient.

NOTE: This information may be provided by NCI.

5.5 Administration

Indicate who will administer the agent, how much should be administered, when it should be taken, whether it should be taken with food and any other instructions for taking the agent.

EXAMPLE:	Subject will self-administer the drug, and will be instructed to take one capsule orally each day, immediately after breakfast.

5.6 Side Effects

Describe toxicity profile and related data for the agent at the selected does and schedule. Informat available from the NCI DCP Clinical Development Plan, Investigational Drug Brochure (if applica the package insert (if applicable) relevant to clinicians participating in this trial may be added to th section. If the amount of information is large, append the relevant information (see Section 17.3).

5.7 Contraindications

Indicate any limitations on medications, herbs, and vitamin and mineral supplements (other than st agents) while participating in the study. Include time periods, if applicable. Also, list restrictions subjects should follow when using the agent (e.g. limit sun exposure).

5.8 Manufacturer and Supplier
Indicate who will provide the agent for the study. NOTE: It is sufficient to note NCI or NCI Repos Contractor as the distributor of the agent, when appropriate.

5.9 Packaging and Labels: Describe in detail how the agent will be packaged. This description should include container(s) (*e.g.*, box, bottle, blister), amount of agent per container (*e.g.*, two bottles per

with 30 capsules in each bottle), the information noted on the label of each container (*e.g.*, subject study number, distributor) and if blinded, how the label will be constructed to maintain the blind (*e* three-part occluded label). In some cases, this information may be supplied by the NCI.

5.10 Storage: Provide instructions regarding proper storage of the agent at study site.

NOTE: These may be provided to the PI by NCI.

EXAMPLE:	Study medication will be stored at room temperature (22.2°C), protected from environmental extremes and in a locked cabinet or room.

5.11 Distribution: Identify the party responsible for dispensing the agent to the subject, and the proced distribution.

EXAMPLE: All study personnel except the pharmacist will be blinded to the study drug treatment.

5.11.1 Run-in procedures:

If a placebo run-in period will occur before randomization to determine subject's compliar describe procedures for the run-in period including administration of placebo, dose, leng period, and timing of assessment of compliance. Compliance should be clearly defined.

5.11.2 Randomization:

For randomized trials, describe the procedure for randomizing a subject to a group.

EXAMPLE:	There will be 2 groups, each consisting of 10 subjects. Following determination of eligibility, each subject will be given a randomization code (if used, the subject will continue to be referred to by his/her unique subject number) and thereby be assigned to a dose group. Subjects will be randomized in a 50/50 ratio to receive agent X or placebo.

5.11.3 Blinding and unblinding methods:

For blinded studies, describe blinding and unblinding methods. Address the following points:

- Procedure for retaining the blind
- Person authorized to break the blind
- Circumstances for breaking the blind
- Procedure for breaking the blind

5.12 Dose Modification: Indicate when and how is it appropriate to reduce the dose of the agent during this study. If applicable, describe procedures for increasing dose after reduction of do due to toxicity.

EXAMPLE:	For grade 1 toxicity or less, no dose modification will be made. For grade 2 toxicity probably or possibly related to drug, dose of study drug will be reduced by 50%. Reduced dose will be maintained until the adverse event (AE) resolves; then drug reintroduced. If the AE recurs, maintain reduced dose for remainder of study. For grade 3 or 4 toxicity probably or possibly related to drug, therapy will be discontinued until toxicity resolves to grade 1 or less. At that time, use of study drug will be resumed at 50% of original dose.

5.13 Adherence/Compliance

5.13.1 Method: Describe the method(s) used to monitor each subject's drug compliance (*e.* medication diaries, pill counts, drug/metabolite plasma levels, and/or drug effect biomarkers).

EXAMPLE: The research staff will evaluate drug compliance using the following means:

1. At each clinic visit, subjects will be given a calendar and instructed to initial it each time a dose is taken.
2. Each subject will be given a bottle containing 30 capsules of study drug at each clinic visit and instructed to return all unused capsules to the investigator. At end of treatment, the actual quantity of unused drug will be compared to the anticipated amount of unused drug and subject calendar.
3. At each clinic visit, the subject will provide a blood sample for evaluation of serum drug level.

5.13.2 Definition: Provide a definition of compliance that will be used to describe which su are considered evaluable (will be included in the statistical analysis as indicated in Se 13.0). (This definition may have implications for the off-study criteria as well, see Section 11.0).

EXAMPLE:	A subject is considered evaluable for determining the effect of study drug if $80% compliance is determined by quantity of unused drug returned to the site and pharmacokinetic analysis indicates a serum drug level of x or greater.

5.14 Drug Accountability: List in detail records that must be maintained regarding receipt, distribu and disposition of study drug. Indicate who will be responsible for maintaining such records.

EXAMPLE:	The investigator is required to maintain adequate records of receipt, dispensing and final disposition of study drug. This responsibility has been delegated to the Pharmacy. Include on receipt record (*e.g.,* packing slip) from and to whom study drug was shipped, date, quantity, and batch or lot number. On dispensing record, note quantities and dates study drug was dispensed to and returned by each subject. At completion of investigation, return all unused study drug to NCI/DCP repository. The record documenting the return of unused drug should include quantity, date, batch or code, and name of the person or department to whom the drug was returned.

5.15 Drug destruction/disposal: indicate procedure for handling the unused drug including: method disposal, documentation of disposal, and any other standard operating procedures relevant to t destruction of investigational agents.

6.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

Delineation of study endpoints and methods for measuring or evaluating them is described here. In chemoprevention studies, endpoints usually fall into the following categories:

Efficacy Endpoints: Depending on the study hypotheses and design, efficacy endpoints may include ar incidence of invasive or preinvasive disease (*e.g.*, polyp incidence); clinical response (*e.g.*, change in r and severity of leukoplakia by physical examination); histologic or cytologic response (*e.g.*, change in severity of dysplasia in biopsy materials); and/or modulation of surrogate endpoint biomarkers (SEBs Define endpoints clearly. Methods for assessment may be described briefly and referenced in this sec

Pharmacokinetics, Safety Studies and Drug Effect Biomarkers: As appropriate, other endpoints (serum/plasma/tissue drug/metabolite levels, other drug effect biomarkers) should be defined clearly. Methods for assessment may be described briefly and referenced in this section with detailed descrip laboratory and computer modeling procedures provided in the Appendix (17.5) “Pharmacokinetic and Biomarker Method Development”.

7.0 CLINICAL EVALUATIONS and PROCEDURES

7.1 Schedule of Events: A table that lists procedures and laboratory evaluations to be performed and when each is to be completed. The table should also indicate when each Case Report From (CR to be completed. A template for the Schedule of Events is included on the following page.

7.2 Pre-intervention Procedures: Describe in detail all procedures that must be completed for a sub before the study intervention can be initiated. Include description of run-in procedures, if applic

7.3 Evaluations during the Study Intervention: Indicate what procedures will be completed, and at w stage of the study, while subject is receiving the study agent(s).

7.4 Evaluations at Completion of Study Intervention: Specify what evaluations must be performed w subject discontinues use of study agent. These evaluations should be consistent with the endpoi described in the objectives and statistical analysis sections of the protocol.

7.5 Follow-up Evaluations: If applicable, specify what evaluations must be performed when a subjec on follow-up. Follow-up is a protocol-specific evaluation period that occurs after the subject st taking the study agent. The section should carefully define and justify the follow-up period for tl protocol. These evaluations should be consistent with the endpoints described in the objectives statistical analysis sections of the protocol.

7.6 Methods for and Clinical Procedures (*e.g.,* Endoscopy, Biopsy): document any special processe instructions, or methodologies for clinical procedures required by the protocol. Include relevan information related to the testing process, for example, instructions for taking study agents if tl requires 'NPO' period; scheduling details for tests which may be available only at certain locati times.

7.0 (continued) **SCHEDULE OF EVENTS TEMPLATE**

Evaluation/Procedures	Screening/ Baseline (Day 0)	Day 1	Week 1	Month 1	Month 3	Month 6/ Termination	Early Withdrawal
Informed Consent	X						
Randomization	X						
On-Study Form	X						
Medical History	X						
Physical Exam	X					X	X
Pregnancy Test	X						
Height/Weight	X	X					
Vital Signs		X	X	X	X	X	X
Serum Chemistry	X			X	X	X	X
Hematology	X			X	X	X	X
Urinalysis	X			X	X	X	X
PK Blood Samples (As applicable)		X				X	X
SEB Measurements (As applicable)	X				X	X	
Adverse Events			X	X	X	X	X
Concomitant Medication		X	X	X	X	X	X
Dispense/Record Study Medication		X	X	X	X	X	X
Off-Study Form						X	X
Compliance Count/ Returned Drug				X	X	X	

8.0 LABORATORY EVALUATIONS and PROCEDURES

8.1 Laboratories: Identify the laboratory(ies) that will perform each analysis for each sample. Whe appropriate, list individuals who will perform analysis and/or procedures for conducting consens reviews of samples.

8.2 Collection and Handling Procedures: For each type of sample obtained (*e.g.,* biopsy, serum), describe the following:

- amount to be collected
- when sample should be obtained (*e.g.,* fasting, prior to A.M. dose)
- processing of sample (*e.g.,* details of tissue fixation, embedding, processing and sectioning
- labeling of sample
- tracking of samples (*e.g.* logs or tracking sheets for subjects)
- temperature storage requirements (*e.g.,* frozen at –20EC).
- storage duration (*e.g.* minimum/maxim length of time)

8.3 Shipping Instructions:

Include this sub-section only if samples must be shipped to an off-site laboratory for analysis. For each sample, describe: packaging (*e.g.,* in a polystyrene container surrounded with dry ice), carrier requirements (*e.g.,* overnight carrier), when samples can be shipped (*e.g.,* Monday throug Wednesday), and name, address and telephone number of the person to whom the samples are be sent.

8.4 Methods for Laboratory Procedures Including Necessary Preparations and Anticipated Risks:

If this information is lengthy, please place in the Appendix (17.4) instead of the body of the pro document.

9.0 REPORTING ADVERSE EVENTS

(Note: Below are subsections to be included in this section of the protocol, along with **recommende language** for each.)

9.1 Definition: An adverse event (AE) is any condition which appears or worsens after the subject is enrolled in an investigational study. Note all adverse events on the Adverse Event Case Report F (CRF), whether or not related to study drug.

9.2 The following information will be collected for all Adverse Events:

- Start and stop dates
- Severity (grade)
- Relationship to study drugs (attribution)
- Whether or not the subject dropped due to the AE

This data is reported on the Adverse Events Reporting Form which is included in the Case Repo Forms set.

9.3 Severity: Adverse events will be graded by a numerical score according to NCI Common Toxici Criteria (CTC), version 2.0 (http://ctep.info.nih.gov/CTC3/default.htm).

NOTE: Situations may arise where the Common Toxicity Criteria, Version 2.0 do not represen certain chemoprevention agent-specific effects, severity of these effects, and attribution of the Examples of this situation include ocular and dermatologic effects associated with retenoids. Therefore, on these occasions the CTC criteria may be expanded or modified to include these situations. The additional criteria should be consistent with those used in earlier studies of the s related agents. Score Adverse Events not included in the defined NCI CTC according to their im on the subject's ability to perform daily activities as follows:

- Mild (causing no limitation of usual activities)
- Moderate (causing some limitation of usual activities)
- Severe (causing inability to carry out usual activities)

The Adverse Events Case Report Form should include this alternate scale as well.

9.4 Follow-up: All AEs, including laboratory abnormalities that in the opinion of the Investigator ar clinically significant, will be followed up according to good medical practices, and documented such.

9.5 **Serious Adverse Events** (SAE): A serious adverse event is defined (by ICH Guideline E2A and Fed. Reg. 62, Oct. 7, 1997) as those events, occurring at any dose, which meet any of the follow criteria:

- Results in death
- Is immediately life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

In addition, events that may not meet these criteria, but which the investigator finds very unusual and/or potentially serious, will also be reported in the same manner.

9.6 **Reporting SAEs**: **In the interest of subject safety in this study and to fulfill regulatory requirements, all Serious Adverse Events, regardless of whether or not it is related to th**

study drug, will be reported to the Sponsor (NCI, DCP) by telephone or fax within 24 ho and in writing within 48 hours, of the investigator learning of the event.
This written information shall be documented on the "NCI Division of Cancer Prevention Serio Adverse Event Form" which can be found in Section 17.6 of this document. In addition all SAEs be entered in the Adverse Event Case Report Form as part of the cumulative report. Prompt foll up reports of the clinical outcome will be sent to NCI.

The contact information for telephone calls and written reports is as follows:

Phone calls or fax within 24 hours of Serious Adverse Events:

Medical Monitor (as specified in the contract)
DCP/National Cancer Institute/NIH
Phone: (301) 496-8563
Fax: (301) 402-0553

Submission of DCP SAE form within 48 hours of Serious Adverse Event to:

Medical Monitor (as specified in the contract)
DCP/National Cancer Institute/NIH
Executive Plaza North, Suite 300
9000 Rockville Pike
Bethesda, MD 20892-7340

Alternate address for Express Mail by hand delivery:

Executive Plaza North, Suite 300
6130 Executive Blvd
Rockville, MD 20852

10.0 CONCOMITANT MEDICATIONS

10.1 Indicate any limitations on medications (other than study drug) while participating in the study. I time periods, if applicable.

EXAMPLE: No ASA or products containing ASA within three weeks of study entry.

10.2 All medications (prescription and over-the-counter),vitamin and mineral supplements, and/or herbs taken by the subject during the study will be documented on a CRF with information including:

- Start and stop dates of drugs, herbs, or supplements
- Dose and route of administration
- Purpose for taking the medication, herbs, or supplements

11.0 OFF- STUDY" CRITERIA

11.1 Study Termination: Specify the criteria for removing a subject from chemoprevention interven from the study protocol. State that NCI, as Sponsor, has the right to discontinue the investigati any time.

EXAMPLE:	The NCI as Sponsor can decide to terminate a subject's participation in the study. This decision could be based on factors such as unacceptable adverse events, lack of Surrogate Endpoint Biomarker modulation on preliminary analysis, *etc.*

11.2 Premature Removal of a Subject: This subsection should define criteria for premature removal subject from the intervention and from the study.

EXAMPLES:

1. Personal reason.
   Note: A subject may withdraw from the study at any time.
2. Non-compliance.
3. Lost to follow-up
   Note: Diligent attempts must be made by telephone and letter to determine the circumstances for loss to follow-up, since such loss may be related to the study drug.
4. Death.

12.0 DATA MANAGEMENT

12.1. Case Report Form Set:

NOTE: The Case Report Form (CRF), a set of forms for each subject, provides a record of data generated according to protocol. These forms are to be completed on an ongoing basis during the st The medical chart is the source of verification of data. During the study, the CRF will be monitore completeness, accuracy, legibility and attention to detail. The CRF will be retained for review.

In this section of the protocol, specify the document on which each of the following is to be record where it is to be sent, and on what schedule. A set of forms may include:

•On-study form
•Eligibility checklist
•Medical history/surgical history
•Physical Examination
•Laboratory data
•Informed consent documents
•Flow sheets and other interim monitoring mechanisms
•Specialty forms for pathology, radiology, or surgery as required
•Symptom and other assessment forms
•Study drug administration/compliance
•Concomitant medications
•Drug calender records
•Adverse Events
•Agent-specific Adverse Events
•Social habits (and changes)
•Efficacy (including biomarker data)
•Physician's notes
•Other forms for interim safety and efficacy evaluations
•Off-study form
•Follow-up summary sheets

NOTE: Please see Appendix V in the DCP Internet Supplemental Information for instructions developing and completing case report forms. Template forms on the web site may be downlo and modified to meet the requirements for individual studies. A WordPerfect file of these for also available available from the DCP Protocol Information Office at (301) 496-0265. The Internet address is: http://pluto4.nci.nih.gov/rfp/DCPPhase2/DCP.htm

12.2 Data Entry, Data Management and Quality Control

Discuss the following information:
- Who will complete the CRF?
- Identify the facility responsible for managing data generated by the study.
- Describe the procedure for data entry (*i.e.*, how data from the CRF will be entered into t database).
- Describe quality control procedures (*e.g.*, double entry, edit or cross checks).
- Describe the format for submitting data to NCI.
- Provide validation documentation of data management system.
- Include standard operating procedures and/or guidelines, if possible.

NOTE: Be sure that appropriate identification is included on every form (*i.e.* no patient names, always include patient and protocol ID numbers). Data capture and reporting is complete. CRF are consistent with protocol and consent form. Data sheets include instructions for completing CRF (schedule on which data sheet is to be completed).

12.3 Progress Reports: State the contract criteria for submission of progress reports. *NOTE: The required format and content for the Quarterly and Annual Progress Reports is found in Appendix I of the DCP Internet Supplemental Information at:* *http://pluto4.nci.nih.gov/rfp/DCPPhase2/DCP.htm*

12.4 Final Report: State the contract deliverables criteria for the submission of draft final and final reports. *NOTE: The required format and content for the Quarterly and Annual Progress Reports is found in Appendix I of the DCP Internet Supplemental Information at:* *http://pluto4.nci.nih.gov/rfp/DCPPhase2/DCP.htm*

12.5 In addition to the quarterly and annual progress reports, the following items are required to be to DCP at the appropriate times during the conduct of the clinical trial.

12.5.1 Protocol revisions and amendments:

- NCI DCP must be notified of proposed protocol amendments to assess impact on trial safety and management of regulatory submission.
- A full copy of the amended protocol must be submitted to DCP for review and approval prior to initiating the changes
- The revised or amended protocol document must be accompanied by a cover sheet detailing the protocol changes, rationale for change, impact on other areas of the protocol, and specific reference to the changed protocol sections.
- The protocol shall be clearly marked with the protocol version number or amendment number
- All protocol amendments must be approved by the Project Officer, Division of Cancer Prevention prior to activation.
- IRB approval documents

12.5.2 Administrative Changes

- Change in Principal Investigator
- Addition of study institutions
- Changes in contact information

13.0 STATISTICAL METHODS

This section should identify the party responsible for analyzing the study data. An adequate statistical s discusses study design in relation to study objectives, and the data evaluation plan, specifically:

13.1 Primary and all secondary hypotheses are clearly stated.

13.2 Sample Size Justification:
Total sample size (including gender and minority considerations) and sampling strategy are described and justified for testing the primary and secondary hypotheses. Power calculations f proposed sample size and endpoints are presented. For comparative studies, differences to be detected are clearly stated and justified with pilot or published data.

13.3 Methods for Randomization and Stratification.
Procedures for randomization and stratification are described and justified. Blocking and/or c techniques used to balance treatment assignment are described.

13.4 Appropriate outcome measures (response rate, time to progression, survival time, etc.) are se and methods for measuring outcomes are described.

13.5 Statistical Analyses:
This section provides a data analysis plan that is logical and appropriate for endpoints selected Plan does not introduce bias through exclusion of participants from analysis. Clinical relevanc the results as well as statistical significance are discussed. Methods of computing confidence intervals for outcome measures are described. Size of expected intervals are indicated.

13.6 Assumptions:
State any assumptions, underlying selection, what they are, are they testable, and method of tes

13.7 Compliance and missing data:
Definition of compliance is clearly stated. Non-compliance is sufficiently addressed. Particu consideration is given to drop-outs, drop-ins and lost-to-follow up. Handling of missing data data from non-compliers are described. Any methods used to impute missing data should be described.

13.8 Interim Analyses:
If relevant to the investigational agent(s) and study design, provides a plan for interim analysis stopping rules. Include plans for monitoring the progress of the trial to implement early termi

13.9 Address analysis of data from ancillary studies, if relevant.

14.0 ETHICAL AND REGULATORY CONSIDERATIONS

(Note: Below are subsections to be included in this section of the protocol, along with **recommend language** for each.)

14.1 Form FDA 1572: Prior to initiating this study, the Principal Investigator will provide a sign Form FDA 1572 stating that the study will be conducted in compliance with regulations fo clinical investigations.

14.2 Institutional Review Board (IRB) Approval: Prior to initiating the study and receiving drug, PI must obtain written approval to conduct the study from the appropriate IRB and NCI. Should changes to study protocol become necessary, protocol amendments will be submitt writing by the PI to the Project Officer (via the DCP PIO) and, when approved, to the IRB f approval prior to implementation.

14.3 Informed Consent: All potential candidates for the study will be given a copy of the study Informed Consent to read. The investigator will explain all aspects of the study in lay langua and answer all the candidate's questions regarding the study. If the candidate decides to participate in the study, he/she will be asked to sign the Informed Consent Document. The s agent(s) will not be released to a subject who has not signed the Informed Consent Docume Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

The informed consent document must be reviewed and approved by the NCI DCP and the IR prior to study initiation. Any subsequent changes to the informed consent must be approvec the NCI DCP and then submitted to the IRB for approval prior to activation.

14.4 Study Monitoring: The FDA and NCI/DCP or their designees may monitor/audit various aspects of the study. These monitors will be given access to facilities, supplies and records review and verify data pertinent to this study. In the situation where the awardee conducts th study monitoring, there must be written policies and procedures describing the monitoring reporting process. These policies must be consistent with policies of the NCI DCP. Furthe information regarding the monitoring process is available at: http://deainfo.nci.nih.gov/grantspolicies/datasafety.htm

14.5 Record Retention: Clinical records for all subjects studied, including CRFs, history and ph findings, laboratory data, and results of consultations, will be maintained by the Investigator secure storage facility and stored until the NCI directs the material to be destroyed.

14.6 Certificate of Confidentiality: See Appendix VI of the DCP Supplemental Internet Informat regarding the appropriate use of Certificates of Confidentiality (http://pluto4.nci.nih.gov/rfp/DCPPhase2/DCP.htm).

15.0 REFERENCES

16.0 SAMPLE INFORMED CONSENT DOCUMENT

Following this page is a modified version of NCI's recommended template for the Informed Consent Documents and instructions for developing an acceptable form. The NCI Recommendations and Con Form Template are available at: http://cancertrials.nci.nih.gov/researchers/safeguards/consent/recs.ht

Participants should be given the opportunity to opt out of allowing their tissues to be collected and st for research that is not part of the protocol. The following web sites present recommendations on inf consent for the storage and use of human tissues for future research studies:

http://bioethics.gov/hbm.pdf
http://www.napbc.org/napbc/nbrpubpr.htm

NOTE: This template will help you develop a consent document that meets both IRB and Federal requirements. Strive to explain this study as you would to an eighth grade student; use short sentences, avoid polysyllabic words, and define all medical terms. When the document is complete, delete all italicized and nonapplicable areas.

INFORMED CONSENT TEMPLATE FOR CHEMOPREVENTION STUDIES (BASED ON NCI TEMPLATE)

NOTE:
- **!** Model text is in **bold**.
- **!** Instructions are in *[italics]*.
- **!** _____ Indicates that the investigator should fill in the appropriate information.

STUDY TITLE

This is a clinical trial (a type of research study). Clinical trials include only persons choose to take part. Please take your time to make your decision. Discuss it with you friends and family.
[Attach NCI booklet "Taking Part in Clinical Trials: Cancer Prevention Studies; What Participants Need to Know" *which can be obtained at* http://cancertrials.nci.nih.gov/understanding/bookshelf/prevention/preintro1.html

You are being asked to take part in this study because you are at increased risk for _ *TYPE OF* cancer.
[Reference and attach information about the type of cancer (and eligibility requirements, if desired).]

WHY IS THIS STUDY BEING DONE?

[Suggestion for applicable text for Phase II studies:]

The purpose of this study is to find out what effects (good and bad) DRUG/INTERVENTIOI **has on you and your** RISK (BIOMARKERS) FOR *TYPE OF* **cancer.**

This research is being done because_

[Explain in one or two sentences. Examples are: **"Currently, there is no effective way to prevent this type of cancer in people at increased risk,"** *or* **"We do not know which o these two commonly-used therapies is better."**]

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

[If appropriate:]
About _____ people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

[Provide simplified schema and/or calendar.]

[For randomized studies:]
You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. Which group you are put in is done by a computer. Neither you nor the researcher will choose what group you will be in. You will have an *EQUAL/ONE IN THREE/ETC.* **chance of being placed in any group.**

[For nonrandomized and randomized studies:]
If you take part in this study, you will have the following tests and procedures:
[List procedures and their frequency under the categories below. For randomized studies, list the study groups and under each describe categories of procedures. Include whether a patient will be at home, in the hospital, or in an outpatient setting. If objectives include a comparison of interventions, list all procedures, even those considered standard.]

! Procedures that are part of regular care *FOR SOMEONE AT INCREASED RISK FOR TYPE OF CANCER* **and may be done even if you do not join the study.**
! Standard procedures being done because you are in this study.
! Procedures that are being tested in this study.

NOTE:
- *Specify how subjects will take the study agent (times/day, dosage, and route), if applicable.*
- *List all paperwork (i.e., diaries, questionnaires) that the subject will be asked to complete.*
- *List specimens to be collected, include frequency and amount.*
- *If specimens will be used for any purpose other than required by the protocol, the intended use must be disclosed and the participant should be given the opportunity to "opt out" of the collection, storage, and use of specimens for non-protocol related purposes.*

HOW LONG WILL I BE IN THE STUDY?

We think you will be in the study for *MONTHS/WEEKS, UNTIL A CERTAIN EVENT* **.**
[Where appropriate, state that the study will involve long-term follow up.]

The researcher may decide to take you off this study if _____.
[List circumstances, such as in the participant's medical best interest, funding is stopped, drug supply is insufficient, patient's condition worsens, new information becomes available.]

You can stop participating at any time. However, if you decide to stop participating in th study, we encourage you to talk to the researcher and your regular doctor first.
[Describe any serious consequences of sudden withdrawal from the study.]

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with th researcher and/or your regular doctor. There also may be other side effects that we cann predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the *INTERVENTION/DRUGS* **are stopped, but in some cases side effects can be serious or long-lasting or permanent.**
[List by regimen the physical and nonphysical risks of participating in the study in categories of "very likely" and "less likely but serious." Nonphysical risks may include such things as the inability to work. Do not describe risks in a narrative fashion. Highlight or otherwise identify side effects that may be irreversible or long-term or life threatening.]

Risks and side effects related to the *PROCEDURES, DRUGS, OR DEVICES* **we are studying include:**
[List risks related to the investigational aspects of the trial. Specifically identify those that may not be reversible.]

[When appropriate]
Reproductive risks: Because the drugs in this study can affect an unborn baby, you shoul not become pregnant or father a baby while on this study. You should not nurse your bab while on this study. Ask about counseling and more information about preventing pregna
[Include a statement about possible sterility when appropriate.]
[Attach additional information about contraception, etc.]

For more information about risks and side effects, ask the researcher or contact _____.
[Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks.]

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit others at risk for *TYP CANCER* **in the future.**

[When appropriate:]

The possible benefits of taking part in the study are the same as receiving *STANDARD DRUG/INTERVENTION* **without being in the study.**

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:
[List alternatives including commonly-used therapy and **"No therapy at this time with routine testing."***]*

[If appropriate (for noninvestigational treatments):]
You may get *STUDY TREATMENTS/DRUGS AT THIS CENTER AND OTHER CENTERS*
even if you do not take part in the study.

Please talk to your regular doctor about these and other options.
[Reference and attach information about alternatives.]

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarant absolute confidentiality. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance data analysis include groups such as:
[List relevant agencies like the National Cancer Institute, Food and Drug Administration, study sponsor, etc.]

If results of the study are presented or published, your name will not be used.

PAYMENT FOR STUDY:

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Plea ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

[If appropriate:]
If, during the study, the *STUDY DRUG* becomes commercially available, you may have to pay for the amount of drug needed to complete the study.

You will receive no payment for taking part in this study. *[or*] **You will receive no payme for the costs of procedures, tests or visits in connection with this research. Costs such as parking fees as a result of participating in this study may be incurred and these costs wil not be covered directly. However, to help defray these costs, you will be reimbursed . . .** *[Specify exactly the amount to be given and how the funds will be distributed over the study period, if applicable.*]

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. If you decide not to take part in the study or if you leave the study afte you agreed to take part, it will not result in any penalty or loss of benefits to which you a otherwise entitled.

We will tell you about new information that may affect your health, welfare, or willingn stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher *NAME* **at** *TELEPHONE NUMBER*.

For questions about your rights as a research participant, contact the researcher *NAME OF CENTER* **Institutional Review Board (which is a group of people who review the research to protect your rights) at** *TELEPHONE NUMBER*. *[And, if available, list patient representative (or other individual who is not on the research team or IRB).]*

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's **Cancer Information Service** at
1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615**

Visit the NCI's Web sites…
cancerTrials: comprehensive clinical trials information **http://cancertrials.nci.nih.gov.**

CancerNet™: accurate cancer information including PDQ **http://cancernet.nci.nih.gov.**

You will get a copy of this form. You may also request a copy of the protocol (full study plan).
[Attach information materials and checklist of attachments. Signature page should be at the end of package.]

SIGNATURE

I agree to take part in this study.

Participant _____ Date _____

17.0 APPENDICES (to the protocol document)

17.1 Sample Case Report Form Set
In the protocol document, please insert the protocol-specific set of case report forms here. See NCI DCP guidelines for completing and designing case report forms located at:
Http://pluto4.nci.nih.gov/RFP/DCPPhase2/DCP.htm

17.2 NCI Common Toxicity Criteria, version 2.0
In the protocol document please insert copy of CTC version 2.0 here. The CTC document may b referenced and downloaded from the following site:
Http://ctep.info.nih.gov/CTC3/default.htm

17.3 Investigational Drug Brochures and Package Inserts

17.4 Methods for Laboratory Procedures:
Including Necessary Preparations and Anticipated Risks:
Specimen Collection, Handling, Transportation, Storage, and Processing;
Drug Metabolite Levels and/or Drug Effect Biomarkers;
Computer-Assisted Image Analysis and Algorithm Development;
Surrogate Endpoint Biomarkers

17.5 Pharmacokinetic and Biomarker Method Development

17.6. Serious Adverse Events: Definition and Report Form
In the protocol document, please insert the instructions for reporting SAE's and the NCI DCP Serious Adverse Report form. A copy of the instructions and form is provided on the following in this document.

Adverse Event Reporting Chart:
Summary of Investigator's Obligations for Reporting
Adverse Events in Phase I–III Clinical Trials to the
National Cancer Institute, Division of Cancer Prevention (DCP)

Reaction	*Reporting Obligation*
a. ALL SERIOUS ADVERSE EVENTS Any adverse event (AE) occurring at any dose that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.	REPORT BY PHONE TO DCP WITHIN 24 HOURS[1] (with written report to follow within 48 hrs[2])
b. ALL ADVERSE EVENTS (SERIOUS, NON-SERIOUS)	REPORTED[3] in the AE CRF and Progress Reports.

[1] Telephone number available 24 hours daily: 301-496-8563 (Recorder after hours); FAX: 301-402-0553 or 301-594-2943.

[2] Report to: **Medical Monitor (as specified in the contract)**
DCP/National Cancer Institute/NIH
Executive Plaza North, Suite 300
9000 Rockville Pike
Bethesda, MD 20892-7540
For Express (*e.g.*, Federal Express, DHL, Airborne) or Hand Delivery

Executive Plaza North, Suite 300
6130 Executive Blvd.
Rockville, MD 20852

[3]A list of all known toxicities can be found in the Investigator's Brochure, package insert, or other material provided by NCI.

NCI Contract/Grant No._____ Study Subject No._____IRB
Protocol No. _____

NCI, DIVISION OF CANCER PREVENTION (DCP)
SERIOUS ADVERSE EVENT FORM

REQUIRED FIELDS ON ALL REPORTS

Today's Date:	Sponsor: NCI, DCP	Study (Indication):
Drug under Investigation:	IND No.:	

A. Study Subject Information

1. Patient Initials	2. Date of Birth: _____ (Month/Day/Year)	3. Weight at Time of Event: _____ [ ] kg [ ] lbs [ ] not available	4. Height at Time of Event: _____ [ ] cm [ ] ft [ ] not available

B. Event Information

[ ] Initial Event Report [ ] Follow-up	Gender: (circle one) M F	Dose at Event:
Event Onset Date: (Month/Day/Year) Event Approx. Time: (indicate A.M./P.M.) Event Occurred at:	Primary Event (diagnosis):	
Duration of Drug Exposure at Event:	Primary Treatment Approx. Time (A.M./P.M.): Primary Treatment of Event:	
Attending Physician (Name): Phone/FAX No.: Hospital/Clinic: Address:		
Describe Event (if applicable, include dates of hospitalization for event):		
Form Completed by: (Print Name) _____ Title_____ Investigator Signature _____ Date _____ Phone No. _____ (Month/Day/Year)		

NCI Contract/Grant No._____ Study Subject No._____IRB
Protocol No. _____

ALL FIELDS APPEARING IN THE FOLLOWING PAGES (C–F) MUST BE COMPLETED FOR THE INITIAL REPORT; THEREAFTER, FILL IN ONLY SECTIONS THAT PROVIDE ADDITIONAL/ CORRECTIVE INFORMATION.

C. Site information

1. Investigator Name
2. Address

D. Suspect Medication(s)

1. Study Design: [ ] Blind [ ] Open/Unblind

Possible Dose (*e.g.*, 300 mg) _____ Frequency (*e.g.*, qd) _____ Route (*e.g.*, po)_____

2. Study Drug	Formulation (*e.g.*, tablet, solution)
	Lot No. (If known)

3. Start Date of Study Drug (Month/Day/Year):

4. Was blind broken due to event? [ ] No [ ] Yes [ ] NA

5. Was Study Drug stopped/interrupted/reduced in response to event? [ ] No [ ] Yes

>> If yes, complete a–e:

a. If stopped, specify date study drug last taken: _____ [ ] NA
(Month/Day/Year)

b. If reduced, specify: New dose _____ Date reduced _____ [ ] NA
(Month/Day/Year)

c. If interrupted, specify total number of days not given: _____ [ ] NA

d. Did event abate after study drug was stopped or dose reduced? [ ] NA [ ] Yes [ ] No

e. Did event reappear after study drug was reintroduced? [ ] NA [ ] Yes [ ] No

6. Was patient taking any other medications concomitantly at the time of the event? [ ] No [ ] Yes >> If yes, complete below.

(DO NOT LIST DRUGS USED TO TREAT EVENT)

Drug Name Doses (units, frequency, route, indication for use)	Start Date			Stop Date or mark (X) if continuing			
	Month	Day	Year	Month	Day	Year	(X)

(continue on a separate sheet if necessary)

NCI Contract/Grant No._____ Study Subject No._____IRB Protocol No. _____

E. Adverse Event

1. Relevant Laboratory/Diagnostic Tests [ ] No tests performed

Date			Test	Results	
				Actual Value	Normal Range
	Month	Day	Year		

(continue on a separate sheet if necessary)

2. Relevant Medical History, including preexisting conditions (*e.g.*, allergies, pregnancy, smoking & alcohol use, hepatic/renal dysfunction, medical/surgical history, *etc.*)

Date (if known)			Diseases/Surgeries/Treatment

(continue on a separate sheet if necessary)

3. **NCI Toxicity GRADE of the Event** (use NCI Common Toxicity Criteria): [ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4
If not gradable by NCI CTC, check one of the following: [ ] Mild (Causing no limitation of usual activities)
[ ] Moderate (Causing some limitation of usual activities) [ ] Severe (Causing inability to carry out usual activities)

4. Why Serious?
[ ] Results in death [ ] Is life-threatening [ ] Requires inpatient hospitalization or prolongation of existing hospitalization
[ ] Results in persistent or significant disability/incapacity [ ] Is a congenital anomaly/birth defect
[ ] Other, specify:_____

5. Outcome of Event (at time of report)

[ ] Resolved–date: _____ [ ] Improved [ ] Unchanged [ ] Worse [ ] Not available
(Month/Day/Year)
[ ] Fatal–date of death: _____ Autopsy performed? Y N
(Month/Day/Year) (circle one)
Cause of death: _____ (please attach death certificate and autopsy report, if applicable)

6. Investigator's opinion of the relationship between the event and the study drug (If more than one event is being reported, list secondary events and corresponding relationship to study drug in the comments section below.) Check applicable box:

[ ] Not related [ ] Unlikely [ ] Possible [ ] Probable [ ] Definite

7. Was this event reported by the Investigator to (check all that apply): [ ] IRB [ ] Manufacturer/Distributor
[ ] Other Investigators participating in this study, if checked, please list names and institutions

_____
_____
_____
_____

NCI Contract/Grant No._____ Study Subject No._____IRB
Protocol No. _____

F. Comments/Clarifications:

FOR NCI USE ONLY
1. Date NCI notified of event (Month/Day/Year):
2. Medical Monitor Review: Medical Assessment of Event (including drug relationship and expectancy):

Is this an FDA reportable (7 calendar days) event? [ ] Yes [ ] No

Is this an FDA reportable (15 calendar days) event? [ ] Yes [ ] No

>> If No, specify reason:_____

Is more information expected? [ ] Yes [ ] No

>> If Yes, specify:_____

Is this event to be communicated to other NCI contractors using this investigational drug? [ ] Yes [ ] No

>> If Yes, how? By telephone (attach a TC Form): [ ] Yes, attached TC Form [ ] No

Other (FAX, mail, e-mail, *etc.*): [ ] Yes, attached a copy of the correspondence [ ] No

Medical Monitor: Print name _____ Signature _____ Date _____